საქართველოს მეცნიერებათა ეროვნული აკადემიის მოამბე, ტ. 13, №4, 2019
BULLETIN OF THE GEORGIAN NATIONAL ACADEMY OF SCIENCES, vol. 13, no. 4, 2019

Organic Chemistry

Synthesis and Mathematical-Chemical Investigation of New Types of N-Glycosylamines

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(Presented by Academy Member Shota Samsoniya)

ABSTRACT. Mathematical chemistry is a new branch of modern theoretical chemistry. By application of the categories of higher algebra (graphs, groups, matrices, etc) it investigates the molecules and their transformations (chemical reactions). The reactions of N-p-carboxyphenyl-β-D-glucopyranosylamine and N-p-carboxyphenyl-β-D-galactopyranosylamine with dicyclohexylcarbodiimide in the presence of tetrahydrofuran and triethylamine have been studied. The interaction of the synthesized N-acylurea with sodium nitrite obtained N-glycosides-N-β-(p-carboxyphenyl-D-glucopyranosyl)-nitrosourea and N-β-(p-carboxyphenyl-D-galactopyranosyl)-nitrosourea containing nitroso (N=O) group. Within the scope of the quasi-ANB-matrix method, mathematical-chemical study of some glycosylamines was carried out. Three conditional correlation equations are constructed. *© 2019 Bull. Georg. Natl. Acad. Sci.*

Key words: mathematical chemistry. quasi-ANB-matrix. triethylamine, glucopyranosylamine, galactopyranosylamine, tetrahydrofuran

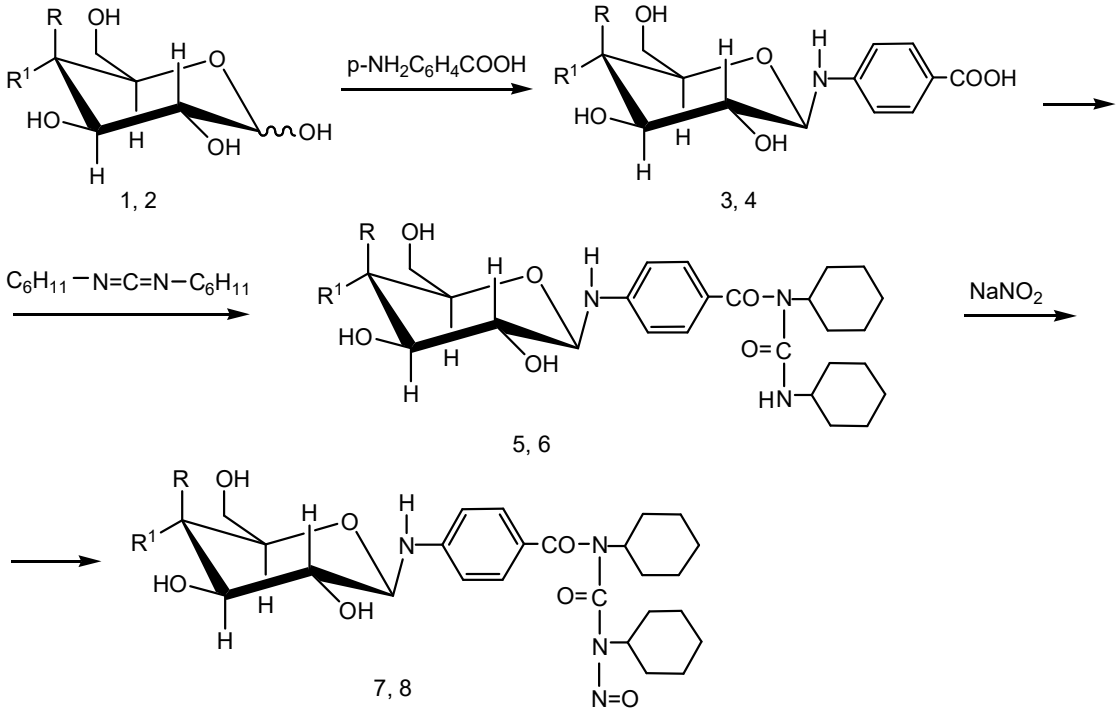
Among the drugs proposed in recent years for the treatment of patients with malignant tumors, the most promising were the derivatives of nitrosourea. Known nitrosoalkylureas (NAU), although they have polarity and can serve as an acceptor in the formation of hydrogen bonds, are nevertheless not hydrophilic enough to provide good solubility in water [1-3].

In this regard, the task of synthesizing the new types of N-glycosides of medicinal substances seems to be very relevant, since glycosylation increases solubility, reduces toxicity, and in some cases changes the nature of the action [4,5].

Recently the growing attention is attracted to the synthesis of the derivatives of nitrosourea. However, the opportunities of all structural modifications of this class of compounds are still not exhausted.

The goal of the present investigation consists in synthesis of N-glycosides containing in a molecule nitrosogroup (N=O). As the starting compound, the condensation product of glucose (1) and galactose (2) with p-aminobenzoic acid-N-*p*-carboxyphenyl-β-D-glucopyranosylamine (3) and N-*p*-carboxyphenyl-β-D-galactopyranosylamine (4) was used [6]. The interaction of the latter under normal conditions of peptide

synthesis with dicyclohexylcarbodiimide in the presence of THF and triethylamine at room temperature, the corresponding acylureas-β-N-(*p*-carboxyphenylglucopyranosyl)-acylurea **(5)** and β-N-(*p*-carboxy-phenylgalactopyranosyl)-acylurea (6). By interaction of compounds **(5,6)** with sodium nitrite corresponding nitrosoderivatives **(7,8)** has been received–β-N-(*p*-carboxyphenylglucopyranosyl)-nitrosourea **(7)** and β- N-(*p*-carboxyphenylgalactopyranosyl)-nitrosourea **(8)** (Scheme).



Scheme. Synthesis of β-N-(p-carboxyphenylgalactopyranosyl)-nitrosourea (8).

The structure of the obtained compounds **5-8** were proved by physico-chemical methods of analysis. Physico-chemical characteristics of the synthesized compounds are given in Table 1. In the ^{13}C NMR spectra of compounds **5-8,** all the corresponding signals of carbon atoms are observed in Table 2.

Table 1. Physical-chemical characteristics of synthesised compounds

Compound	Brutto formulas	Was found% Was calculated%			$T_{melt.}$°C	$[\alpha]_D^t$ (c, EtOH)	The yield (%)
		C	H	N			
5	$C_{26}H_{37}N_3O_7$	62.02 / 61.9	7.35 / 7.82	8.84 / 8.35	146-147	–34.6° (0.41, t=17°)	59.4
6	$C_{26}H_{37}N_3O_7$	61.43 / 61.9	7.61 / 7.82	7.97 / 8.35	162-163	–44.8°(0.39, t=17°)	52.8
7	$C_{26}H_{36}N_4O_8$	58.44 / 58.02	6.7 / 7.08	10.83 / 10.53	132-134	–27.3° (0.59, t=18°)	62.4
8	$C_{26}H_{36}N_4O_8$	57.73 / 58.02	7.51 / 7.08	10.98 / 10.53	154-155	–41.9° (0.44, t=17°)	52.3

Table 2. C^{13}NMR spectra of compounds 5-8

N	Chemical Shifts ($CDCl_3$), δ, ppm
5	85.76 (C-1); 74.02 (C-2); 78.51 (C-3); 72.18 (C-4); 76.44 (C-5); 59.72 (C-6). Aromatic nucleus: 150.58(C-1); 113.40 (C-2); 130.22 (C-3); 117.70 (C-4); 131.20 (C-5); 111.35 (C-6); 167.5-170.0 (C=O); 12.5-23.0 ($\underline{C}H_2$).
6	92.7 (C-1); 79.3 (C-2); 77.54 (C-3); 77.0 (C-4); 76.6 (C-5); 62.5 (C-6). Aromatic nucleus: 151.40(C-1); 112.50 (C-2); 130.00 (C-3); 116.80 (C-4); 132.10 (C-5); 110.30 (C-6); 166.0-168.5 (C=O); 12.0-22.8 ($\underline{C}H_2$).
7	87.82 (C-1); 71.12 (C-2); 76.60 (C-3); 69.52 (C-4); 74.83 (C-5); 61.8 (C-6). Aromatic nucleus: 150.32(C-1), 112.20 (C-2),129.85 (C-3), 116.40 (C-4); 130.80 (C-5); 111.22 (C-6); 168.5-172.0 (C=O);12.0-25.5 ($\underline{C}H_2$).
8	98.6 (C-1); 76.4 (C-2); 74.8 (C-3); 74.3 (C-4); 72.4 (C-5); 63.2 (C-6). Aromatic nucleus: 149.20 (C-1); 112.33 (C-2); 131.84 (C-3); 119.70 (C-4); 130.72 (C-5); 111.00 (C-6); 169.5-174.0 (C=O); 13.8-24.6 ($\underline{C}H_2$).

The synthesized compounds were studied within the scope of mathematical chemistry basis of quasi-ANB-matrices method: Quasi-ANB matrix is modified form of the contiquity matrix of molecular graph [6-8]. Diagonal elements of quasi-ANB-matrix are the atomic numbers of the chemical elements, nondiagonal ones are the multiplicities of the chemical bonds [9, 10].

For the glucose derivatives under study, the simplest model was developed:

$$X - Y,$$

where: X ≡ H, NO; Y – remain fragment of the molecule.

Corresponding quasi-ANB – matrix has a form:

$$\left\| \begin{matrix} Z_X & 1 \\ 1 & Zy \end{matrix} \right\|$$

Three conditional equations were derived:

$T_{melt.} = -11.9 \mathrm{Lg}\,(\Delta_{QANB}) + 174.7$

$[\alpha]_D^{17} = -6.2\ \mathrm{Lg}\,(\Delta_{QANB}) + 48.6$

$R_f = -0.09\ \mathrm{Lg}\,(\Delta_{QANB}) + 0.94$

After synthesing new compounds real correlation equations can be constructed.

Experimental

H^1NMR spectra were recorded in $CDCl_3$ on a Bruker WM-250 spectrometer (250 MHz) with TMS internal standart. C^{13}NMR spectra were recorded on a Bruker AM-300 (75,5 MHz) in $CDCl_3$. The optical rotation was measured on SU-3 universal saccharimeter at 20 ± 2^0C. IR spectra were obtained in KBr disk on a UR-20 spectrometer. The purity of products and R_f values were determined on Silufol UV-254 using solvent systems $CHCl_3$:CH_3OH (19:1, system a), C_6H_6:$CH_3COOC_2H_5$ (2:1 system b), C_6H_6:$CHCl_3$ (2:1, system c), C_6H_6:$CHCl_3$ (4:2, system d). The preparation N-*p*-carboxyphenyl-β-D-glucosyl(galactosyl)amine (3,4) has been reported [5].

N-*p-carboxyphenyl*-β-D-glucosylamine (3). Yield (90%), mp. 125.5-127^{0}C, R_f 0.53(system d), $[\alpha]_D^{20}$ -77.8^0 (c 0.64, ethanole) [5].

N-p-carboxyphenyl-β-D-galactosylamine (4). Yield (85.8%), mp. 151-153^{0}C, R_f0.41(system d), $[\alpha]_D^{20}$ -52.5^0 (c 0.4, pyridin) [5].

β-N-(*p*-carboxyphenylglucopyranosyl)-acylurea (5). To a solution of 0.6 g(0.002 mole) N-β-carboxyphenyl-D-glucopyranosylamine in 20 ml of tetrahydrofuran under cooling up to 0°C and stirring was added 0.52g (0.002 mole) dicyclohexylcarbodiimide and 0.4 ml triethylamine. Mixture was stirred for 2 h and kept in the refrigerator for 20 hours. Sediment was filtered out and after treatment with activated carbon solvent was removed by vacuum stripping. The residue was dissolved in chloroform, washed by 5% solution of citric acid, water and dried over Na_2SO_4. After filtration, chloroform was evaporated and residue was treated with petroleum ether at simultaneous rubbing with stirring rod. Recrystallized from ethanol. Yield 0.59(59.4%), mp. 146-147^{0}C, R_f 0.72 (system a), $[\alpha]_D^{17}$ -34.6^0 (c 0.41, C_2H_5OH). Found,%: C 61.9; H 7.82; N 8.04. $C_{26}H_{37}N_3O_7$. Calculated,%: C 62.02; H 7.35; N 8.35.

IR spectrum (ν, cm^{-1}): 2840, 2935 (CH_2–cyclohexanole), 3230 (NH), 3300-3400 (OH), 760, 820, 900 (Benzol), 1380, 1430 (CO – NH), 1510 (CO-N<), 1720 (C=O), 3080 (C-H_{arom}).

H^1 NMR spectrum (δ, ppm, J/Hz), TMS: 5.50 (1H, d, $J_{1,2}$ = 8.0, H-1), 4.94 (1H, dd, $J_{2,1}$ = 8.0, $J_{2,3}$= 9.5, H-2), 5.20 (1H, dd, $J_{3,2}$ = 9.5, $J_{3,4}$ = 3.0, H-3), 4.30 (1H, dd, $J_{4,3}$ = 3.0, $J_{4,5}$ =9.5, H-4), 3.80 (1H, ddd, $J_{5,4}$ = 9.5, $J_{5,6'}$ = 5.0, $J_{5,6''}$ = 2.5, H-5), 4.06 (1H, H-6 ', dd, $J_{6',6''}$ = 12, $J_{6'5}$ = 2.5,), 4.20 (1H, H-6", dd, $J_{6'6''}$ = 12, $J_{6''5}$ = 5.0,), 1.8-0.8 (20 H, m, 10C<u>H</u>$_2$ cyclohexyl), 7.0 (1H, m, N<u>H</u>), 7.5-7.8 (4H, m, aromatic group), 3.1 and 4.1 (2H, s, C<u>H</u>=N<u>H</u>).

C^{13} NMR spectrum (δ, ppm), $CDCI_3$: 85.76 (C-1), 74.02 (C-2), 78.51 (C-3), 72.1 (C-4), 76.44 (C-5), 59.72 (C-6), 167.5-170.0 (C=O), 12.5-23.0 (CH_2-cyclohexyl). Aromatic group: 150.58 (C-1), 113.40 (C-2), 130.22 (C-3), 117.70 (C-4), 131.20 (C-5), 111.35 (C-6).

β-N-(*p*-carboxyphenylgalactopyranosyl)-acylurea (6) was prepared analogously. Yield 0.52 (52.8%), mp. 162-163.5^{0}C, R_f 0.49 (system c), $[\alpha]_D^{17}$ -27.3^0 (c 0.39, C_2H_5OH). Found,%: N 7.93. $C_{26}H_{37}N_3O_7$. Calculated,%: N 8.35.

IR spectrum (ν, cm^{-1}): 2935 (CH_2–cyclohexanole), 3319 (NH), 3340 (OH), 764, 920 (Benzol), 1700-1600 (CO – NH), 1529 (CO – N<), 1715 (C=O), 3060 (C-H_{arom}).

H^1 NMR spectrum (δ, ppm, J/Hz), TMS: 5.70 (1H, d, $J_{1,2}$ = 8.0, H-1), 4.94 (1H, dd, $J_{2,1}$ = 8.0, $J_{2,3}$= 9.5, H-2), 5.22 (1H, dd, $J_{3,2}$ = 9.5, $J_{3,4}$ = 3.0, H-3), 4.40 (1H, dd, $J_{4,3}$ = 3.0, $J_{4,5}$ =9.5, H-4), 3.84 (1H, ddd, $J_{5,4}$ = 9.5, $J_{5,6'}$ = 5.0, $J_{5,6''}$ = 2.5, H-5), 4.22 (1H, H-6 ', dd, $J_{6',6''}$ = 12, $J_{6'5}$ = 2.5,), 4.03 (1H, H-6", dd, $J_{6'6''}$ = 12, $J_{6''5}$ = 5.0,), 1.8-1.2 (20 H, m, 10C<u>H</u>$_2$ cyclohexyl), 7.1 (1H, m, N<u>H</u>), 7.3-7.5 (4H, m, aromatic group), 2.6 and 4.32 (2H, s, C<u>H</u>=N<u>H</u>).

C^{13} NMR spectrum (δ, ppm), $CDCI_3$: 92.7 (C-1), 79.3 (C-2), 77.54 (C-3), 77.0 (C-4), 76.6 (C-5), 62.5 (C-6), 166-168.5 (C=O), 12.0-22.8 (CH_2-cyclohexyl). Aromatic group: 150.40 (C-1), 112.5 (C-2), 130.0 (C-3), 116.80(C-4), 132.10 (C-5), 112.5 (C-6).

β-N-(*p*-carboxyphenylglucopyranosyl)-nitrosourea (7). To a solution of 0.2 g (0.0003mole) of compound **5** in 1 ml of glacial acetic acid and 2 ml of acetic anhydride under cooling up to 0°C and stirred for 2 hours was added portionwise 0.5, the $NaNO_2$.The mixture was kept for 20 hours in the refrigerator

and then was processed in cold water with ice cubes. Solid matter repeatedly was extracted with ether. Ether extract was washed with water, dried over Na_2SO_4 and the solvent was evaporated under vacuo. The residue, which is yellowish powder mass, was treated with petroleum ether and recrystallized from ethanol. Yield 0.13 (62.4%), mp. 132-134^{0}C, R_f0.62 (system b), $[\alpha]_D^{18}$ - 27.3^0 (c 0.59, C_2H_5OH). Found,%:

C 58.02; H 7.08; N 10.81. $C_{26}H_{36}N_4O_8$. Calculated,%: C 58.64; H 6.76; N 10.53.

IR spectrum (ν, cm^{-1}): 2938 (CH_2–cyclohexanole), 3339 (NH), 2990-3300 (OH), 761, 910 (Benzol), 1495 (CO – N<), 1715 (C=O), 3060 (C-H_{arom}), 1525 (-CO-N-N=O), 1020 (-N-N-)

H^1 NMR spectrum (δ, ppm, J/Hz), TMS: 5.42 (1H, d, $J_{1,2}$ = 8.0, H-1), 5.30 (1H, dd, $J_{2,1}$ = 8.0, $J_{2,3}$= 9.5, H-2), 5.05 (1H, dd, $J_{3,2}$ = 9.5, $J_{3,4}$ = 3.0, H-3), 5.20 (1H, dd, $J_{4,3}$ = 3.0, $J_{4,5}$ =9.5, H-4), 3.80 (1H, ddd, $J_{5,4}$ = 9.5, $J_{5,6'}$ = 5.0, $J_{5,6''}$ = 2.5, H-5), 4.0 (1H, H-6 ', dd, $J_{6',6''}$ = 12, $J_{6'5}$ = 2.5,), 4.16 (1H, H-6", dd, $J_{6'6''}$ = 12, $J_{6''5}$ = 5.0,), 1.8-1.0 (20 H, m, 10C$\underline{H}_2$ cyclohexyl), 7.1-7.5 (4H, m, aromatic group), 3.25 and 4.1 (2H, s, C$\underline{H}$=N$\underline{H}$).

C^{13} NMR spectrum (δ, ppm), $CDCI_3$: 87.82 (C-1), 71.12 (C-2), 76.60 (C-3), 69.52 (C-4), 74.83 (C-5), 61.8 (C-6), 168.5-172.0 (C=O), 12.0-25.5 (CH_2-cyclohexyl). Aromatic group: 150.32 (C-1), 112.20 (C-2), 129.85(C-3), 116.40 (C-4), 130.8 (C-5), 111.22 (C-6).

β-N-(*p*-carboxyphenylgalactopyranosyl)-nitrosourea (8) was prepared analogously. Yield 0.11 (52.3%), mp. 154-155^{0}C, R_f0.59 (system d), $[\alpha]_D^{17}$ – 41.9^0 (c 0.44, C_2H_5OH). Found,%: N 9.98; $C_{26}H_{36}N_5O_8$. Calculated,%: C N 10.53.

IR spectrum (ν, cm^{-1}): 2850, 1440 (CH_2–cyclohexanole), 3310 (NH), 3330 (OH), 760 (Benzol), 1480 (CO – N<), 1690 (C=O), 3060 (C-H_{arom}), 1520 (-CO-N-N=O), 1080 (-N-N-).

H^1 NMR spectrum (δ, ppm, J/Hz), TMS: 5.64 (1H, d, $J_{1,2}$ = 8.0, H-1), 5.08 (1H, dd, $J_{2,1}$ = 8.0, $J_{2,3}$= 9.5, H-2), 5.21 (1H, dd, $J_{3,2}$ = 9.5, $J_{3,4}$ = 3.0, H-3), 5.32 (1H, dd, $J_{4,3}$ = 3.0, $J_{4,5}$ =9.5, H-4), 4.14 (1H, ddd, $J_{5,4}$ = 9.5, $J_{5,6'}$ = 5.0, $J_{5,6''}$ = 2.5, H-5), 3.86 (1H, H-6 ', dd, $J_{6',6''}$ = 12, $J_{6'5}$ = 2.5,), 3.72 (1H, H-6", dd, $J_{6'6''}$ = 12, $J_{6''5}$ = 5.0,), 1.8-1.0 (20 H, m, 10C$\underline{H}_2$ cyclohexyl), 7.4-7.7 (4H, m, aromatic group), 2.8 and 4.2 (2H, s, C$\underline{H}$=N$\underline{H}$).

C^{13} NMR spectrum (δ, ppm), $CDCI_3$: 98.6 (C-1), 76.4 (C-2), 74.8 (C-3), 74.3 (C-4), 72.4 (C-5), 61.8 (C-6), 169.5-172.4 (C=O), 13.0-24.4 (CH_2-cyclohexyl). Aromatic group: 149.20 (C-1), 112.33 (C-2), 131.84(C-3), 119.70 (C-4), 130.72 (C-5), 111.00(C-6).

ორგანული ქიმია

ახალი ტიპის N-გლიკოზილამინების სინთეზი და მათემატიკურ-ქიმიური გამოკვლევები

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(წარმოდგენილია აკადემიის წევრის შ. სამსონიას მიერ)

მათემატიკური ქიმია თანამედროვე თეორიული ქიმიის შედარებით ახალი განხრაა. უმაღლესი ალგებრის კატეგორიების (გრაფები, ჯგუფები, მატრიცები და სხვ.) გამოყენებით მათემატიკური ქიმია იკვლევს თეორიული ქიმიის პრობლემებს – ქიმიურ სტატიკას (მოლეკულებს) და ქიმიურ დინამიკას (რეაქციებს). პირველად იქნა შესწავლილი N-β-(p-კარბოქსიფენილ-β-D-გლუკოპირანოზილამინისა და N-β-(p-კარბოქსიფენილ-β-D-გალაქტოპირანოზილამინის რეაქცია დიციკლოჰექსილკარბოდიიმიდთან ტეტრაჰიდროფურანში ტრიეთილამინის თანაობისას. მიღებული აცილშარდოვანების-N-β-(p-კარბოქსიფენილ-D-გლუკოპირანოზილ)-აცილშარდოვანისა და N-β-(p-კარბოქსიფენილ-D-გალაქტოპირანოზილ)-აცილშარდოვანის მოქმედებით ნატრიუმის ნიტრიტთან, სინთეზირებულია ნიტროზო (N=O) ჯგუფის შემცველი N-გლიკოზილამინები: N-β-(p-კარბოქსიფენილ-D-გლუკოპირანოზილ)-ნიტროზოშარდოვანა და N-β-(p-კარბოქსიფენილ-D-გალაქტოპირანოზილ)-ნიტროზოშარდოვანა. კვაზი-ანბ-მატრიცების ფარგლებში ჩატარდა ზოგიერთი N-გლიკოზილამინის მათემატიკურ-ქიმიური კვლევა. აგებულია სამი კორელაციური განტოლება. კორელაციები დამაკმაყოფილებელია.

REFERENCES

1. Perevodchikova N. I.., Korman N. P., Bychkov M. B. (1975) Lechenie bol'nykh rakom legkogo kombinatsiei nitrozometilmocheviny i tsiklofosfana. *Voprosy onkologii,* **21,** 8: 21-40 (in Russian).

2. Rapoport I. A. (1948) Deistvie okisi etilena, glitsida, glikolei na gennye mutatsii. *Doklady akademii nauk SSSR,* **60,** 3: 469-472 (in Russian).

3. JohnsonT .P., Mc CalebG.S., Montgomery J.A. (1975) Synthesis of chlorozotocin, the 2-chloroethyl analog of the anticancer antibiotic streptozotocin *J. Med. Chem*., 18: 104-106.

4. Stepanenko B. N., Volkova E. S., Chentsova M. G. (1967) Sintezy nekotorykh N-karboksifenil- i N-khlorfenilglikozilaminov. *Doklady akademii nauk SSSR,* **177**, 3: 607 (in Russian).

5. Sidamonidze N.N., VardiashviliR.O., Onashvili K.Z., Tabatadze L.V. (2018) Synthesis and bactericidal properties sulfur-containing 1,2-trans-glycosides. *Black sea. Scientific Journal of Aademic Research,* **41,** 3: 35-40.

6. Gverdtsiteli M.I., Gamziani G.A., Gverdtsiteli I.M. (1996) The Contiguity Matrices of Molecular Graphs and their Modifications. Tbilisi (in Georgian).

7. Sidamonidze. N.N., Kupatadze K.T., Gverdtsiteli M.I. (2009) Theoretical study of the "structure-property" correlation within the framework of the ANB, quasi-ANB and EP-matrix methods. *Applied Physics,* 6: 36-40.

8. Sidamonidze N.N., Gverdtsiteli M.I. (2016) Grafy: "Simmetrichnaia zvezda", "psevdo- simmetrichnaia zvezda", "assimmetrichnaia zvezda" i ikh primenenie v matematicheskoi khimii. *Engineering Physics. Inzhenernaia fizika,* 6: 94-98 (in Russian).

9. Tabatadze L. V., Sidamonidze N. N., Phachulia Z. V., Shengelia N. G. (2018) Synthesis and Quantum-chemical modeling of 2-O-(β-D glucopyranosyl)-α, D-mannopyranose. *Black sea. Scientific Journal of Academic Research,* **40,** 02: 40–52.

10. Gverdtsiteli M. I., Machaidze Z. G., Sidamonidze N. N. (2016) Matematiko-khemicheskoe issledovanie elektroprovodimostei Ph_4PCI i Ph_4PBr v spirtovykh rastvorakh. *Engineering Physics. Inzhenernaia fizika,* 10: 65-67 (in Russian).

Received July, 2019